CCR frontiers IN SCIENCE

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Contents

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■ CLINICAL RESEARCH

Clinical Trials Highlights: Head and Neck Cancers

Head and neck cancers—cancers of the oral cavity, salivary glands, paranasal sinuses and nasal cavity, pharynx, larynx, and lymph nodes in the upper part of the neck—account for 3% of all cancers in the United States. Nearly 38,000 Americans developed one of these cancers in 2002. Unfortunately, morbidity due to head and neck cancers is high.

NCI offers three treatment trials for patients with head and neck cancers, which are often called "squamous cell carcinomas" because most of these cancers arise in the flat, squamous cells that line the structures of the head and neck. For information on these and other studies taking place at NCI, contact the Clinical Studies Support Center at 1-888-NCI-1937.

Because head and neck surgery to remove cancer may affect a patient's ability to chew, swallow, or talk and may affect a patient's appearance, rehabilitation and supportive care are an important part of treatment. Supportive care is free to patients in these trials.

01-C-0104
Carter Van Waes, M.D.

A Phase I Study of PS-341 and Radiotherapy in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Part of a family of drugs called dipeptidyl boronic acids, PS-341 is a new anticancer drug that is administered concurrently with radiotherapy to potentially increase the effect of the radiotherapy. PS-341 targets proteasome enzymes, which play an important role in breaking down proteins that regulate the cell cycle. The drug inhibits the breakdown of these proteins, which in turn leads to death of the cancer cells. PS-341 has already produced promising effects in multiple myeloma and prostate cancer. Eligible patients should have squamous cell carcinoma of the head and neck. It should be at least 4 weeks since they last had surgery or chemotherapy and 6 weeks since they last had radiotherapy. There should be no metastasis to the brain. On this protocol, patients receive PS-341 twice weekly on Mondays and Thursdays. They also receive radiotherapy daily from Monday through Friday. Treatment continues for 6 to 8 weeks, depending on the amount of radiotherapy previously received. Patients are evaluated once a week for 2 months and then once a month for 1 year.

01-DC-0006
Erik S. Kass, M.D.

A Phase I/Pilot Study of a Recombinant Virus Vaccine in Patients with Advanced Squamous Cell Carcinoma of the Head and Neck

Surgery, chemotherapy, and radiation therapy have long been the hallmarks of cancer treatment. Biological therapies, which attempt to harness the body's own immune system to combat cancer, are now under investigation as well. NCI and the National Institute of Deafness and Other Communication Disorders (NIDCD) are offering patients with advanced head and neck cancers a recombinant (i.e., genetically engineered) fowlpox virus vaccine called rF-TRICOM. Eligible patients should have measurable squamous cell carcinoma of the oral cavity or the oropharynx accessible for intra-oral injection, metastatic or recurrent

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If you have scientific news of interest to the CCR research community, please contact the scientific advisor responsible for your area of research, Tracy Thompson, or Sue Fox.

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disease following surgery and/or radiation, no more than two prior chemotherapy regimens, no treatment for at least 4 weeks, and no history of metastasis to the central nervous system. Patients will undergo staging endoscopy, biopsy, and an intratumoral injection of rf-TRICOM, then receive a "booster" vaccine of rf-TRICOM at 3 weeks and 8 weeks after the initial injection.

00-C-0128
Edward A. Sausville, M.D.

A Phase II Study of Flavopiridol in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Flavopiridol, one of a family of drugs known as flavanoids, is under investigation as an anticancer drug. Preclinical *in vivo* tumor models suggest that flavopiridol may inhibit cellular proliferation, thus causing significant tumor regression. Eligible patients should have squamous cell carcinoma of the head and neck and either metastatic disease at diagnosis, or metastatic or recurrent disease after surgery and/or radiation therapy. Patients must not have nasopharynx tumors and must not have a history of central nervous system disease. They should have no more than one prior chemotherapy regimen for recurrent or metastatic disease. Patients accepted into the protocol receive flavopiridol as a 1-hour intravenous infusion on days 1 through 5. Patients then return home for days 6 through 21. Treatment repeats every 21 days in the absence of disease progression or unacceptable toxicity.

BIOTECHNOLOGY RESOURCES

Microarrays Lead the Way: A Powerful Research Tool for the Post-genomics Era

The new millennium ushered in what may also be considered a new millennium for *Homo sapiens*' biological research. Shortly into the year 2000 the International Human Genome Sequencing Consortium and Celera Corporation announced they had sequenced the entire human genome, which is composed of more than 3,000,000,000 bits of information (base pairs of nucleotides). Our genetic makeup, however, was found to contain not much more than 30,000 genes (still a controversial result), a relatively small number considering the lowly nematode has about 19,000 genes and rice has nearly 50,000 genes.

This wealth of genomic information enables researchers to study the expression and function of every gene in the human body. But how does one analyze the expression of 30,000–50,000 genes at one time? The answer lies in microarray technologies that debuted in the mid-1990's but only recently came into widespread use. The microarray field is a good example of the assemblage and convergence of several technologies, including DNA sequencing, PCR, oligonucleotide synthesis, robotics, miniaturization, nucleic acid labeling chemistries, and bioinformatics. A microarray may be thought of as a miniaturized gene hybridization and detection assay. Instead of measuring signals in assays at the "macro" level (such as one finds in microtiter plates, membrane blots, test tubes, and so on), individual microarray assays or elements are measured in microns (one millionth of a meter). A reasonable size for such "micro-elements" is approximately 100 microns, as opposed to about 0.5–1.0 cm (5,000–10,000 microns) for dimensions at the bottom of wells in microtiter plates. One platform for printing microarrays is the common microscope slide with dimensions of 25 x 75 mm; 50,000 spots or elements can easily fit on a slide if the spots are 100 microns in diameter and spacing between each element is 50 microns. Thus, it is possible to place the entire human gene complement on one slide, an accomplishment that was impossible only a decade ago.

Each element contains the DNA sequence from one gene and is used to measure the expression of its corresponding messenger RNA (mRNA) in a cell or tissue. mRNA from experimental samples are used to synthesize fluorescently labeled complementary DNA probes, which are then hybridized to the microarray spots or elements. The fluorescent signal of the hybridized probes is measured with a laser scanner capable of detecting emission from a variety of fluorescent molecules. The intensity of the signal is directly correlated with the original concentration of the mRNA in the cell or tissue; thus, by measuring the signal one can deduce whether the expression of a particular gene is upregulated, downregulated, stays the same, or is even expressed at all. The sensitivity is very good: microarrays can detect the presence of one mRNA (out of 100,000) per cell. This technique allows investigators to study the expression of thousands of genes at one time in the cell or tissue type of their choice.

The sequence of most of the human genes is now known, but the function of probably less than half have been determined and advances in medical research will be delayed without the determination of the structure and function of these genes. Microarrays will provide a pivotal and powerful research tool. The use of microarrays at the NCI is expanding rapidly and already has resulted in several landmark publications in cancer research. The findings from this type of research will result in more effective and radically new ways of treating (and curing) cancer. Microarrays will be used to characterize all cancers by determining what genes—normal and mutated—are expressed in tumors and at what levels, which will lead to understanding how cancer cells differ from their normal counterparts and ultimately point the way to new targets and therapies. This technology will also be used in the clinic as a diagnostic and prognostic tool so that each patient could have personalized or tumor-specific therapies. Thus, the clinical oncology lab of the 21st century will be a molecular oncology lab and microarrays will be an integral part of it.

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■ RETROVIRUSES

Getting a "Grip" on Reverse Transcription: Ribonuclease H Activity and Alteration of Cleavage Specificity

This is the second in a series of three articles focusing on the role of RNase H primer grip region in HIV reverse transcription.

Rausch JW, Lener D, Miller JT, Julias JG, Hughes SH, and Le Grice SFJ. Altering the RNase H primer grip of human immunodeficiency virus reverse transcriptase modifies cleavage specificity. *Biochemistry* 41: 4856-65, 2002.

As in all retroviruses, HIV-1 replication requires synthesis of a double-stranded DNA copy of the plus-strand viral RNA genome. This process is catalyzed by a single virus-encoded reverse transcriptase (RT) that possesses DNA- and RNA-dependent DNA synthesis and ribonuclease H (RNase H) activities. HIV-1 minus-strand DNA synthesis initiates from a host-derived $tRNA^{Lys3}$ primer annealed near the 5' terminus of the viral RNA, and continues following transfer of the nascent DNA strand from the 5' to the 3' end of the genome. After

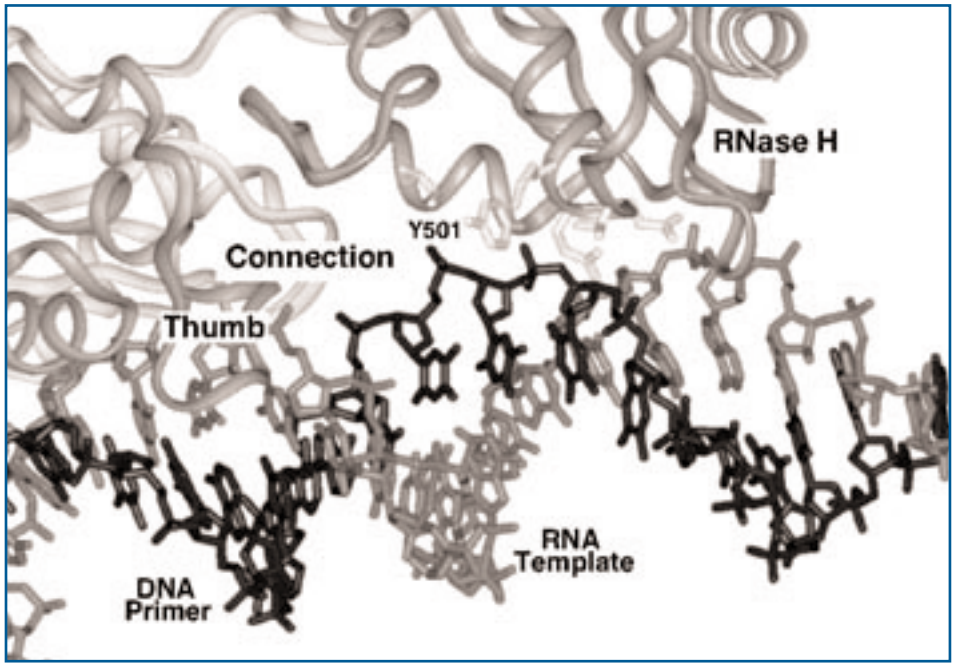

Figure 1. Ribbon diagram illustrating RNase H primer grip residues of the HIV-1 RNase H domain. For simplicity, portions of p51 reverse transcriptase in the vicinity of the p66 RNase H domain were omitted. The p66 thumb and connection, in addition to its C-terminal RNase H domain, are indicated. For orientation, RNase H primer grip residue Tyr501, contributing to the specificity of PPT recognition, is highlighted. Primer and template nucleotides of the RNA/DNA hybrid are indicated in black and grey, respectively.

RNase H-mediated cleavage of the viral RNA, synthesis of plus-strand DNA initiates from two purine-rich RNA fragments referred to as the 3' and central "polypurine tracts" (PPTs). The double-stranded viral DNA is completed following a second template switch, strand displacement DNA synthesis, and RNase H-mediated removal of minus- and plus-strand primers.

Much effort has been directed towards understanding the mechanism by which each step of reverse transcription is accomplished. In particular, the means by which RT precisely cleaves at the 3' termini of, but not at sites internal to, the PPTs has yet to be determined. Recently, X-ray crystallographic data indicated that several residues within the connection subdomain and C-terminal RNase H domain of the HIV-1 RT p66 subunit make important contacts with an RNA/DNA hybrid containing the HIV-1 3' PPT (Sarafianos SG, et al., *EMBO J* 20: 1449-61, 2001). These residues, collectively referred to as the "RNase H primer grip," include T473, N474, E475, K476, Y501, and I505 as well as H539 within the RNase H domain. In the current study, the authors conducted a mutational analysis of these residues in recombinant HIV-1 RT to determine how amino acid substitution at these positions affects template-primer binding, DNA synthesis, RNase H activity, minus-strand transfer, and PPT selection and removal.

Except for the I505G mutation, which exhibited a dimerization defect, substituting alanine at positions 473-476 and 501 slightly reduced DNA synthesis activity on DNA and RNA templates. In contrast, the efficiency with which most mutants catalyzed "polymerization-independent" RNase H cleavage was sharply reduced. More specifically, cleavage at the primary RNA cleavage site 18 nucleotides removed from the recessed DNA 3' terminus in an RNA/DNA hybrid was relatively unaffected by amino acid substitutions within the primer grip, whereas cleavage at the secondary (or polymerase-independent) RNA cleavage site (8 nucleotides removed) was drastically reduced.

Deficiency in RNase H-mediated cleavage was more pronounced when mutant enzymes were challenged to process the plus-strand 3' PPT from either plus-strand RNA or a PPT/plus-strand DNA (RNA/DNA chimera), particularly when alanine was substituted at position 501. Not only was cleavage at the PPT 3' terminus reduced, but cleavage specificity was altered. Finally, reduced polymerization-independent RNase H activity adversely affected the rate of DNA strand transfer, suggesting that the donor template must be shortened to fewer than 13 nucleotides before this event proceeds.

These results provide strong evidence that the RNase H primer grip is an important determinant of *in vitro* RNase H activity and RNase H cleavage specificity. The results are consistent with the notion that these contacts with the DNA primer help to properly position the template-primer at the RNase H active site.

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MOLECULAR BIOLOGY

A Two-edged Sword: Roles for p38 Mitogen-activated Protein Kinase in Cell Cycle Control in Normal and Malignant Cells

Bulavin DV, Higashimoto Y, Popoff IJ, Gaarde WA, Basrur V, Potapova O, Appella E, and Fornace AJ Jr. Initiation of a G2/M checkpoint after UV radiation requires p38 kinase. *Nature* 411: 102-7, 2001.

Bulavin DV, Saito SI, Hollander MC, Sakaguchi K, Anderson CW, Appella E, and Fornace AJ Jr. Phosphorylation of human p53 by p38 kinase coordinates N-terminal phosphorylation and apoptosis in response to UV radiation. *EMBO J* 18: 6845-54, 1999.

To maintain the integrity of a multicellular organism, cells must continuously respond to changes in the extracellular environment. Diverse extracellular stimuli—including ultraviolet light irradiation, heat shock, high osmotic stress, proinflammatory cytokines, and certain mitogens—trigger a stress-regulated protein kinase cascade culminating in activation of p38 mitogen-activated protein kinase (p38 MAPK). This activation results in a variety of different changes, including regulation of transcription, protein synthesis, cell surface receptor expression, and regulation of the cell cycle proteins, thereby ultimately affecting cell survival. Because of the changes it can initiate, p38 MAPK has been implicated in pathogenesis of different diseases, such as sepsis, ischemic heart disease, arthritis, human immunodeficiency virus infection, and Alzheimer's disease. Thus, specific p38 MAPK inhibitors may ultimately offer therapeutic benefit for certain critically ill patients.

Evidence exists of a role for p38 MAPK in the positive regulation of proliferation of certain types of cells. Recent

Because of the changes it can initiate, p38 MAPK has been implicated in pathogenesis of different diseases, such as sepsis, ischemic heart disease, arthritis, human immunodeficiency virus infection, and Alzheimer's disease. Thus, specific p38 MAPK inhibitors may ultimately offer therapeutic benefit for certain critically ill patients.

extensive analysis in our laboratory and by others of the cell cycle-related functions of p38 MAPK has demonstrated that this kinase has an additional role: the negative regulation of the transition from the G2 phase to mitosis (Wang X, et al. *Mol Cell Biol* 20: 4543-52, 2000; Bulavin DV, et al. *Nature* 411: 102-7, 2001; Dmitrieva NI, et al. *Proc Natl Acad Sci U S A* 99: 184-9, 2002; Bulavin DV, et al. *Curr Opin Genet Dev* 92-7, 2002). Similar to Chk1 kinase, a well-known regulator of the cell cycle, p38 MAPK seems to play a prominent role in G2/M checkpoint activation after certain types of stress. The p38 MAPK is able to maintain phosphorylation of Cdc25B phosphatase at serine 309 (Bulavin DV, et al. *Nature* 411: 102-7, 2001). This phosphorylation induces Cdc25B to interact with the inhibitory protein 14-3-3 and displace Cdc2 kinase from the complex. Thus, Cdc2 kinase—necessary for cell cycle progression—undergoes inhibitory phosphorylation and remains inactive, thereby preventing progression into mitosis.

A physiological example is osmotic stress in renal epithelial cells. Survival of proliferating renal epithelial cells under continuous osmotic stress requires functional checkpoints. Inactivation of p38 MAPK under these conditions allows cells that have not reached the G2/M border to progress into mitosis even if they are not ready for the next phase of the cell cycle (Dmitrieva NI, et al. *Proc Natl Acad Sci U S A* 99: 184-9, 2002). When p38 MAPK activity is inhibited for an extended period, this progression causes significant cell death *in vitro* and can compromise kidney function *in vivo*.

No less important is the role for p38 MAPK as a negative regulator of cell proliferation by activation of the p53 tumor suppressor (Bulavin D, et al. *EMBO J* 18: 6845-54, 1999). Because it is critically involved in regulating serine 33 and 46 phosphorylation of p53, p38 MAPK could play an important role in regulating apoptosis under different conditions, including oncogene-induced apoptosis. In this case, modulation of p53/p38 MAPK-dependent pro-apoptotic functions could be important in tumor suppression, although direct *in vivo* evidence is still missing. Further experimentation will be required to show whether p38-mutant mice exhibit increased tumorigenesis. However, it has recently been found that amplification of the gene encoding the Wip1 phosphatase occurs frequently in human breast cancer with wild-type p53 (Bulavin DV, et al. *Nat Genet* 31: 210-5, 2002). Wip1 phosphatase inactivates p38 MAPK, which leads to reduced p53 activation. Thus, Wip1 can act as an oncogene presumably by inhibiting p38 MAPK, which functions as a tumor suppressor in this case.

On the basis of the above observations, one can speculate that, depending on the genetic background and probably the cell type, p38 MAPK could either suppress or promote tumor formation. In this scenario, if p53 remained wild type and Cdc25B functions were not compromised, activation of p38 MAPK would ultimately lead to inhibition of cell proliferation, protecting the multicellular organism from unregulated cellular division. On the other hand, if p53 were inactivated (by mutations, gene silencing, or other possible mechanisms) and Cdc25B phosphatase were overexpressed, p38 MAPK would be expected to lose these important inhibitory functions and could positively regulate proliferation, thus promoting tumor development in certain cell types. Under these conditions, inhibition of p38 may improve therapy for select tumors.

Undoubtedly, the beneficial effects of p38 MAPK inhibitors could be an important part of anti-inflammatory therapy. Yet the possible dual function of p38 MAPK raises an additional concern for extended therapy with such inhibitors, because inhibition of p38 MAPK may contribute to tumor promotion and renal toxicity.

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Concept-based Clinical Trials: Translating Basic Discoveries into the Clinic

This is the second part of a two-part series focusing on concept-based clinical trials.

Many of the CCR's concept-based trials take advantage of the richly diverse patient populations attracted to the NIH Clinical Center. That diversity permits clinical investigators to accrue patients with rare malignancies, those belonging to specific ethnic or racial groups, and those with specific genetic profiles. The Genetics Branch plays a role in patient recruitment for many trials involving patients with specific genetic mutations. For example, the Branch has recently finished accrual for a trial in which individuals with an altered nucleotide mismatch repair gene provided multiple biopsies. This archive will permit researchers to explore the biological basis underlying the predisposition to develop hereditary non-polyposis colorectal cancer and to investigate whether the pattern of gene expression can be used to predict responses to therapeutic, chemopreventive, or environmental agents.

CCR concept-based trials also explore and validate the clinical utility of new technologies. High-throughput microarray technologies for genomic and proteomic profiling show increasing promise as diagnostic, prognostic, and predictive tools. In early 2000 researchers in the Metabolism Branch, using the Lymphochip (a customized cDNA microarray) to measure gene expression in tumors from patients with diffuse large B-cell lymphoma (DLBCL), announced that DLBCL comprises two molecularly distinct diseases that radically differ in their response to chemotherapeutic agents. This study was among the first to demonstrate that molecular profiling could play a direct and clinically useful role in refining diagnosis and guiding treatment selection. The Metabolism Branch is now participating in the Lymphoma/Leukemia Molecular Profiling Project, an effort to reclassify human lymphoid malignancies according to their molecular characteristics. The objectives are to define molecular correlates of clinical parameters and use this information to select appropriate therapies. A Phase II trial is being launched to investigate the effectiveness of PS-341, an agent that blocks a pathway involved in drug resistance, in DLBCL patients who relapse following standard chemotherapy.

Having launched the Clinical Proteomics Program, investigators in the Laboratory of Pathology have developed a novel high-throughput microarray technology—the reverse-phase protein array coupled with laser capture microdissection—to provide molecular profiles of signaling pathways involved in cancer progression and to track changes in such pathways in cancer patients before, during, and after treatment. Four early-phase clinical studies are being conducted to assess the efficacy of proteomics-based technology for early diagnosis, patient prognosis, early detection of tumor recurrence, and treatment evaluation. Because preliminary results have demonstrated that serum-based proteomic pattern analysis can detect early-stage ovarian cancer with 100% sensitivity and 95% specificity, a trial will soon be launched that will acquire ovarian tissue samples on a large-scale basis to explore the feasibility of using this technology for mass screening. Another study will seek to develop a protein profile indicative of relapse for patients with advanced-stage peritoneal, fallopian tube, or ovarian epithelial cancer and patients with stage IIc clear cell cystadenocarcinoma.

Refractory and understudied diseases represent another focus of the CCR's concept-based trials. Targeting biological mechanisms giving rise to drug resistance, such as the human multi-drug resistance gene (MDR-1), represents an especially promising avenue for developing therapies effective against refractory disease. Using clinical samples taken from patients with drug-resistant acute lymphoblastic leukemia, the Experimental Therapeutics Section of the Cancer Therapeutics Branch (CTB) has demonstrated that chemotherapy-induced chromosomal rearrangements can cause overexpression of MDR-1. The mutagenic effects can be attenuated by modulating the chemotherapy schedule—a finding directly relevant to clinical practice. A current Phase I protocol involves the use of XR9576, a novel, highly potent modulator of p-glycoprotein, which is overexpressed on the surface of MDR^+ tumor cells. Pre-clinical studies indicate that XR9576 can potentiate the cytotoxicity of several chemotherapeutic drugs, including doxorubicin, paclitaxel, and vincristine.

Among programs designed to elucidate the biology and treatment of hitherto-understudied cancers, the NCI Kidney Cancer Program, led by the Urologic Oncology Branch and encompassing a kidney cancer working group made up of more than 60 investigators from 18 laboratories and branches, is unparalleled. The working group has completed a Phase II study of a molecularly targeted monoclonal antibody, bevacizumab, in patients with kidney cancer. Bevacizumab exerts anti-angiogenic effects by targeting vascular endothelial growth factor; many treated patients exhibited significant tumor shrinkage, thus validating the clinical viability of this anti-angiogenic approach. Research into the genetics of renal carcinomas and the development of molecularly targeted therapeutics has been a central priority of the Branch for more than a decade. During the 1990's, investigators identified three genes that, when mutated,

cause three distinct types of kidney cancer, including the *VHL* gene, which causes sporadic clear cell renal carcinoma. A trial is under way to determine the efficacy of a vaccine containing tumor-specific mutated VHL peptides.

More than one-third of the CCR's clinical studies are designed to delineate the effects of novel molecularly targeted agents on signal transduction pathways active in cancer cells, especially when used as part of combination regimens. Many kinase inhibitors are undergoing early-phase trials. One agent is flavopiridol, a cyclin-dependent kinase inhibitor that has advanced into Phase II trials involving patients with late-stage metastatic malignancies. Two epidermal growth factor receptor kinase tyrosine inhibitors are being scrutinized: the Metabolism Branch is assessing the effects of ZD-1839 administered in combination with Taxol and radiation therapy to patients with squamous cell carcinomas of the head and neck, and the CTB is evaluating the molecular end points associated with OSI-774 by using serial biopsies from patients with metastatic breast cancer.

Histone deacetylase inhibitors represent an intriguing new class of drugs that reverse the silencing of gene expression resulting from histone modification. The CTB Molecular Therapeutics Section is conducting Phase I and II studies of the potent histone deacetylase inhibitor depsipeptide to treat cutaneous and peripheral T-cell lymphoma. To date, 15 of 21 patients with mature T-cell lymphoma have responded to the agent, and 2 are in continuous complete remission. These studies also indicate that depsipeptide reaches its nuclear target.

Although the CCR's concept-based clinical trials have proved to be an extraordinarily successful means of translating basic discoveries into the clinic, certain challenges remain. Among the most important issues is the researchers' regulatory burden. Rigorous reviews of the quality of the science and careful scrutiny of measures taken to protect patients' safety are, of course, indispensable to maintaining the CCR's scientific and public credibility. But protocol development and approval—from the initial filing with the Food and Drug Administration through multiple layers of reviews by NIH and extramural agencies, all of which must occur sequentially—take far too long and often discourage investigators initially eager to participate in the clinical trial process. It should be possible to streamline the process without sacrificing scientific rigor or ethical safeguards.

■ J. Carl Barrett, Ph.D.

■ ADMINISTRATIVE LINKS

Gift Giving at NIH

Gifts given within the office are governed by law. As a federal employee, you should be aware of the limitations on gift giving in the office. To learn more, request a copy of the Office of General Counsel's "Gifts Between Employees" pamphlet from your local NCI Ethics Office (http://camp.nci.nih.gov/public/ethics/index.html).

Property Inventory Policies

NIH has completed the 2002 physical inventory of property. Reports of Survey (HHS 342) have been given to the property custodians to distribute to the employees responsible for the missing property. These users are required to exaplin why the equipment was not found and return the form to the NCI Property Staff. The 2003 property inventory is scheduled to begin in mid-February. If you have any questions, please contact Mike Lundell (301-435-2063) or Susan Connors (301-492-6002) or see the property chapter in the NCI Administrative Directory (http://camp.nci.nih.gov/admin/directory/topic/top9.htm).

Computer Security at NIH

A number of new computer security measures have recently been implemented at NIH as part of the HHS, NIH, and NCI efforts to improve information technology security. These changes have included new HTTP and FTP security policies, MS SQL Server and NetBIOS firewall blocks, and new DNS registration procedures. To learn more, please visit the following sites:

- Network security: NCI Wireless network, NIH VPN, DNS registration, and firewall policies (http://camp.nci.nih.gov/support/sec/http-dns.html).
- General computer security: recommendations and resources for securing Windows computers (http://camp.nci.nih.gov/support/sec/sec_coresvcs.html).
- Unix security: recommendations and resources for securing Unix computers (http://camp.nci.nih.gov/support/sec/sec_unix.html).
- Other useful computer links: guidance on SPAM, chain letters, hoaxes, security listservs, and other practical computer advice (http://camp.nci.nih.gov/support/sec/sec-links.html).

CCR Intranet Home Page

Bookmark this URL! The new CCR Intranet Home page, http://ccrintra.cancer.gov/default.asp, lists many important links on one convenient page, including the following:

- Resource Request System (RRS) for submitting your IRA, CPA, and letters of intent for budget meetings.
- PI/Lab Content Management System (CMS) to update your PI and lab Web pages online.
- Faculty listservs to send an e-mail to all the members of your faculty.
- Faculty Meeting Request Form to obtain help in planning your next faculty retreat, seminar, or workshop.
- Fellows Editorial Board to learn about editing help for post-docs and clinical fellows.
- Media Techniques for Scientists, containing tips, policies, and media training information for PIs who talk with the mass media.
- Institutional Review Board (IRB), containing important information on NCI human subjects research.
- NCI Combined Intramural PI Retreat links to the agenda, registration, abstract submission, and other information regarding the retreat.

ON THE TENURE TRACK

Karlyne Reilly, Ph.D.

A native of Berkeley, California, Karlyne Reilly, Ph.D., transplanted to the east coast in 1986 to attend Yale University. She graduated *magna cum laude* with a B.S. in molecular biophysics and biochemistry, using biochemical approaches to study the stability of transmembrane alpha helices under Dr. Donald Engelman. From Yale, Dr. Reilly continued on to Harvard University to complete her Ph.D. thesis under Dr. Douglas Melton. As a National Science Foundation graduate fellow, she studied mesoderm induction and axial patterning in the frog (*Xenopus laevis*). This graduate work formed the foundation of her current interests in vertebrate model systems and the importance of the intact cell microenvironment and cell-cell interactions in biological processes.

With a background in biochemistry and molecular biology, Dr. Reilly made the move from the tetraploid frog model system to the more genetically tractable mouse model system for her postdoctoral studies in Dr. Tyler Jacks' laboratory at the Massachusetts Institute of Technology. She applied her background in developmental biology to the study of tumorigenesis, thinking about cancer as an essentially developmental process with evolving steps of initiation and progression. With the sequencing of the human and mouse genomes, she became interested in the role of the genome in an individual's susceptibility to cancer. Whereas her graduate work had focused on drawing parallels between frog, mouse, and human development, Dr. Reilly's post-doctoral work focused on how polymorphisms between different individuals affect tumor development. As a post-doctoral fellow of the Leukemia and Lymphoma Society, the American Association for Cancer Research—Sidney Kimmel Foundation, and the American Cancer Society, she developed a model system to examine the role of modifier genes on the malignancies associated with neurofibromatosis type 1. By examining the effects of mutations in the *Nf1* and *p53* genes on different mouse strains, she identified a new mouse model of astrocytoma and demonstrated that the tumor spectrum of *Nf1:p53* compound mutant mice depends on the strain background.

Dr. Reilly joined the Mouse Cancer Genetics Program of the CCR in March of 2002 as a tenure-track principal investigator. Her group focuses on identifying the modifier genes that affect malignancies associated with neurofibromatosis type 1, with an emphasis on astrocytoma. Dr. Reilly is also using her model of astrocytoma to investigate the mechanism of tumor progression and infiltration. She is continuing her emphasis on the interaction between cells and their intact environment within animal model systems, and how this interaction affects cellular behavior such as infiltration.

Dr. Reilly lives with her husband, two young daughters, and not-so-young dog in Potomac, MD. She enjoys hiking and canoeing along the C&O canal with her family, and loves oil painting whenever she gets a chance. Her favorite color is bromophenol blue or ultramarine blue, depending on which hemisphere of her brain she is currently exercising.

Dr. Reilly

INTRAMURAL RESEARCH FACULTY WEB SITES

In 2001, the NCI announced the formation of Faculties composed of scientists from diverse laboratories and branches working cooperatively with a common interest in a particular discipline, disease, or approach to scientific discovery. Faculties provide mechanisms to enhance and enable collaborations, interdisciplinary research, and translational (bench-to-bedside) science. Faculties

- Enhance and enable communications among basic, clinical, and epidemiological researchers,
- Support retreats, seminar series, and visiting scientists,
- Promote collaborative interdisciplinary research,
- Enhance the translation of basic research into the prevention and treatment of cancer,
- Facilitate mentoring and recruitment of fellows and improve training opportunities,
- Facilitate the development of and provide access to core infrastructure and new technologies, and
- Advise NCI leadership on important and innovative programmatic directions for NCI.

Web sites have been established for 14 Faculties thus far, and links to each of these sites can be found on the Faculty home page at http://ccr.cancer.gov/faculties/. Information on the goals, events, projects, and members can be found on each Web site.